

PATENT
PC7250AMEB

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF: : EXAMINER:
DOUGLAS J. M. ALLEN ET AL. :
CONTINUATION OF: :
SERIAL NO.: 07/449,961 : ART UNIT:
FILED: DECEMBER 21, 1992 :
FOR: AZITHROMYCIN DIHYDRATE :

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Hon. Commissioner of Patents and Trademarks
Washington, D.C. 20231

Sir:

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correspondence is being
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20231, on this 28th day of

DECLARATION UNDER 37 C.F.R. § 1.132

By Joseph G. Burch

I, Helen R. Hangac, declare that:

1. I received a Ph.D. degree in Analytical Chemistry
from Duke University in 1982.

2. I have been employed by Pfizer Inc, assignee of
the above-identified application, in the Analytical
Research and Development Department at Groton, Connecticut
since 1982. My current position is that of project leader
in which I am responsible for analytical procedures
performed on experimental pharmaceuticals, including
azithromycin.

3. I am familiar with the subject matter of the
above-identified application.

4. A series of experiments were performed under my
direction by Near Infrared Spectroscopy and X-ray Powder
Diffraction to determine if significant amounts of
azithromycin dihydrate (Type A) were present in
azithromycin (Type B) a hygroscopic monohydrate. The
azithromycin (Type B) lots examined/used in the studies
are listed in Table 1. The azithromycin (Type B) lots
utilized in the experiments were manufactured using three
different crystallizing solvent systems, i.e.,
ethanol/water, acetone/chloroform, and acetone. All lots
of azithromycin (Type B) listed in Table 1 have been shown
to be equivalent using infrared spectrometry, and/or X-ray

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diffraction and are equivalent to the original sample described by Bright in U.S. Patent 4,474,768.

AZITHROMYCIN TYPE B LOTS EXAMINED/USED IN NEAR IR AND X-RAY STUDIES		
LOT NUMBER	TYPE	SOLVENT SYSTEM
1022107	TYPE B	ACETONE/CHLOROFORM
4351080	TYPE B	ACETONE/CHLOROFORM
1039117	TYPE B	ACETONE/CHLOROFORM
4101026	TYPE B	ETHANOL/WATER
13,577-209-1F	TYPE B	ETHANOL/WATER
4101036	TYPE B	ACETONE/CHLOROFORM
17,419-216-3	TYPE B	ACETONE
11,860-18-1 ¹	TYPE B	ETHANOL/WATER
¹ Sample referenced in Bright, U.S. Patent 4,474,768, Example 3.		

5. I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

April 19, 1994
Date

Helen H. Hargac
Helen H. Hargac

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF: : EXAMINER: J. BROWN
DOUGLAS J. M. ALLEN ET AL. :
SERIAL NO.: 07/449,961 : ART UNIT: 183
FILED: DECEMBER 11, 1989 :
FOR: AZITHROMYCIN DIHYDRATE :

Hon. Commissioner of Patents and Trademarks
Washington, D.C. 20231

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Commissioner of Patents and
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20231, on this 19th day of
December 19 92.

Sir:

DECLARATION UNDER 37 C.F.R. 1.119

I, George A. Forcier, declare that:

1. I received a Ph.D. degree in Analytical Chemistry
from the University of Massachusetts in 1966.

2. I have been employed by Pfizer Inc, the assignee of
the above-identified application since 1966. My current
position is that of Group Director, Analytical Research and
Development Department. Part of my responsibility is the
supervision and direction of analytical procedures performed
on experimental pharmaceuticals, including azithromycin.

3. I am familiar with the subject matter of the above-
identified application.

4. I am familiar with the impact which the physical
and chemical properties of experimental drugs have on the
commercial potential of the product.

5. Hygroscopicity tests on azithromycin dihydrate
(Type A) and azithromycin "monohydrate" (Type B) were
performed under my direction and supervision. Azithromycin
"monohydrate" is a crystalline solid that exists as a non-
stoichiometric hydrate because of its hygroscopic nature.
The dihydrate (Type A) is a discrete crystalline compound.

6. Example 1, p. 7 of the above-identified application
correctly describes the hygroscopic behavior of azithromycin
dihydrate at relative humidity of 18%, 33%, 75% and 100%.
This experiment was done under my direction and supervision.

7. Preparation 1, p. 9 of the above-identified
application correctly describes the hygroscopic behavior of

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azithromycin monohydrate at relative humidities of 18%, 33%, 75% and 100%. This experiment was done under my direction and supervision.

8. The significance of Example 1 and Preparation 1 lies in the fact that azithromycin dihydrate maintained the constant water content of the dihydrate (4.6%) at relative humidities of 33% and 75% over a 3 day period. In contrast, the monohydrate increased water content from the theoretical value of 2.6% to 6.6% at 75% relative humidity and 5.6% at 33% relative humidity.

9. A side by side test comparing the relative hygroscopicity of azithromycin dihydrate and monohydrate was conducted under my supervision and direction. Two lots of monohydrate were compared with two lots of dihydrate at 75% relative humidity for 120 hours. The monohydrate was found to gain about six times more water than the dihydrate as shown in the table below.

HYGROSCOPICITY OF AZITHROMYCIN AT 75% RELATIVE HUMIDITY Weight Gain (%)				
Time (hour)	Monohydrate Lot 209-1F	Dihydrate* Lot 76-1	Dihydrate Lot 274-1	Monohydrate Lot 82-1
0	0.00	0.00	0.00	0.00
2	0.94	- 0.21	0.21	1.58
5	1.04	- 0.20	0.35	1.72
24	1.28	- 0.11	0.39	1.86
48	1.26	- 0.06	0.34	1.81
70	1.25	+ 0.06	0.34	1.81
120	1.13	- 0.20	0.19	1.69

*The weight loss is believed to be due to mechanical loss of very fine powder of this sample when the weighing bottles were opened and closed.

10. Lack of hygroscopicity is an important advantage in a pharmaceutical product. Hygroscopic azithromycin (Type B) has poor handling properties, such as poor flowability and adhesiveness to equipment surfaces, and is susceptible to

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water content changes during processing and storage at ambient conditions. Accretion of even small amounts of water often makes formulation difficult or impossible because of these poor handling properties and an inability to place a constant amount of active ingredient in each tablet or capsule.

11. The lack of hygroscopicity of azithromycin dihydrate was an important consideration in selecting this material for commercialization.

12. I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Date:

March 19, 1997

George A. Forcier
George A. Forcier

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